REMARKS

Claims 1-4 and 13-14 were rejected pursuant to 35 U.S.C. §112, first paragraph.

Applicant respectfully submits that this rejection should be withdrawn for the following reasons.

Applicant is submitting a Declaration by Dr. Fisher simultaneously with this Response.

The Examiner has contended that because there are certain cells where Mi would be present that are not malignant cells the assay would not distinguish between melanoma cells and these cells. The Examiner also contends that there is nothing in the claims that imposes such a requirement to distinguish between cells.

Applicant respectfully disagrees. Step (b) of claim 1 requires that the skilled artisan determine (i) if Mi is being expressed and (ii) if Mi is being expressed in a malignant cell. This is explicitly required in the phrase "wherein the expression of Mi in a malignant cell is indicative of melanoma." Thus, the first part of Step (b) teaches that binding by the probe is indicative of Mi expression, but the claim further teaches that it is an expression of Mi in a malignant cell that is indicative of melanoma. Applicant respectfully submits that the claim clearly teaches the skilled artisan that they have to determine whether the Mi is being expressed in a malignant cell or not. Accordingly, the discussion in the previous Amendment about the ability to distinguish malignant cells from non-malignant cells by a wide range of means was, indeed, relevant to the claims.

As Applicant previously discussed, it is easy to determine whether a sample contains malignant cells or not. In Dr. Fisher's Declaration (unexecuted copy attached), he discussed this

in more detail. The claims are written to the person of skill in the art, and the skilled artisan would recognize that they would not look at a single point in isolation but rather rely on the state of the art and that collective body of data to arrive at a diagnosis (See, Paragraphs 6 and 7 citing Chapter 13 of the textbook Cancer: Principles in Practice of Oncology, Fourth Edition (1993)).

The skilled artisan has a number of ways to distinguish between malignant cells and normal cells. For example, osteoclasts are multi-nucleated, whereas melanoma cells are not. Mast cells are filled with granules, whereas melanoma cells are not. Melanocytes are not invasive cells. Thus, simply by looking at the specimen, the skilled artisan could distinguish them. With respect to cells such as benign nevus and dysplastic nevus cells, there are standard dyes that will readily provide differential staining of malignant cells as opposed to non-malignant cells (See, Fisher Declaration, Paragraph 9).

Thus, Applicant respectfully submits that one could readily determine if there is a malignant cell expressing Mi.

The Examiner further contends that even if Applicant were to include a limitation drawn to distinguishing melanoma from other possible tumors that would result in a rejection of the claims under 35 U.S.C. §112, first paragraph. The Examiner cites to page 2 of the Application. Applicant respectfully submits that the Examiner's statement is wrong and appears to be taking single sentences out of the entire context of the specification. For example, the Background starts at page 1 with the discussion that melanoma has been on the rise for decades (See, Page 1, line 16-28). The second paragraph further teaches that metastatic diseases of unknown origin are fairly common, and melanoma resides among the tumor types most commonly associated with metastasis lacking an obvious primary tumor site. The specification goes on to teach that it has

proven difficult to determine if such metastatic tissue is melanoma. Thus, at page 1, the problem is stated. Melanoma is on the rise but it has proven difficult to determine if a metastatic tissue which can be one of numerous different tumor types is melanoma. It is then pointed out that there are two markers that have been used to identify tumors as melanoma but that they have other problems and that there is a need for other markers that will detect melanoma (See, Page 2, line 6-7). It is then pointed out in the next paragraph that determining the origin of a metastatic tissue arising from a melanoma is extremely difficult and that it is important to know the origin because it can effect the diagnosis and treatment. All of this discussion, however, is based on the difficulty of determining whether a particular malignant cell is a melanoma as opposed to a different tumor. It is explicitly taught at page 6 that Applicant has discovered that there is a high correlation between the presence of Mi in a malignant cell and that cell being a melanoma, and Applicant has looked at numerous malignant cells and found that Mi can distinguish melanoma from other tumors. For example, among malignant tissues that it does not stain are basal cell carcinomas, squamous cell carcinomas, atypical fibroxanthoma, granular cell tumor, schwannoma and neurofibroma. Thus, Applicant respectfully submits that the specification clearly teaches and supports that one can use this marker to distinguish melanoma from other possible tumors.

Moreover, it is respectfully submitted that the Examiner's discussion about the two non-melanoma tumors that stained positive for Mi is simply a non-sequitor. Applicant taught that the current markers being used to determine whether or not a particular tumor was a melanoma have a number of deficiencies, and Applicant compared the present marker against those markers. It was never claimed that this marker is 100% accurate, and indeed, the claim does not say that.

The claim language is that the presence of Mi in a malignant cell is **indicative** of a melanoma. In real life, one is never talking about 100% absolutes (See Fisher Declaration, Paragraph 10).

Moreover, to put those results discussed by the Examiner in context, one must remember that it was 2 out of 81 cases where there was some staining, and in fact, there was no nuclear staining. Thus, the data the Examiner is discussing was seen in only about 2.5% of the cases. Moreover, as shown in Figure 7, 8 and Table 1, the probe of the present invention is much more sensitive and specific than the markers currently being used, and it is not just the Applicant saying that those markers were the current standard, but as explained in Paragraph 12 of Dr. Fisher's Declaration, the field pointed to those other markers. (See, Fisher Declaration, Paragraphs 10, 12 and 13).

Now the field is looking to the present marker (See Fisher Declaration, Paragraph 14). Accordingly, Applicant respectfully submits that the office has no basis for disregarding the teaching of the present specification and that the claims fully comply with 35 U.S.C. §112.

Claims 1-4 and 13-14 were also rejected pursuant 35 U.S.C. § 112, first paragraph. The Examiner has contended that Applicant has not distinguished between the various Mi isoforms and that only the M isoform is known to be associated with melanoma.

Applicant has taught that the presence of Mi in a malignant cell is indicative of melanoma. The Examiner has cited nothing to question that teaching. The Examiner has cited nothing that suggests that the A or H isoform would be present in a malignant cell that is not a melanoma. Thus, her distinguishing between the different isoforms with respect to the claim language has nothing to do with the present teaching. Rather, the Examiner seems to be to trying to require the Applicant to use a probe that is only specific for the M isoform. Applicant taught a

probe for Mi and that such a probe would work. Applicant taught that one looks for the presence of Mi in malignant cells. Applicant provided substantial exemplification of malignant cells where Mi was present and provided substantial back up data in the Application. Thus, by using the teaching of the specification, one can readily generate probes for Mi that are present in malignant cells and use such probes to screen other samples. Thus, given the extensive exemplification, the teaching of how to make and use the description therein, the claims fully comply with 35 U.S.C. § 112 (See, Fisher Declaration, Paragraph 15).

Claim 3 was rejected pursuant to 35 U.S.C. § 112, first paragraph.

Applicant respectfully submits that this rejection should be withdrawn.

The Application teaches that one can use a probe that detects the presence of mRNA expressing Mi in malignant cells. As explained in the Fisher Declaration, Paragraph 16, which cites to Du, J., AJP, 164:333-343 (2003), Applicant's teaching has been verified. Thus, the fact that in a minority of cases there may not be a correlation between mRNA expression and an immunohistochemistry approach that situation does not exist here. The teaching of the specification works as taught.

Accordingly, Applicant respectfully submits that this rejection of the claim should be withdrawn.

In view of the foregoing, the Applicant respectfully submits that all claims are in condition for allowance. Early and favorable action is requested.

Respectfully submitted,

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